Original Article

Microalbuminuria and low hemoglobin as risk factors for the occurrence and increasing severity of diabetic retinopathy

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Aim: To assess the influence of urinary microalbuminuria and hemoglobin concentration on the occurrence and severity of diabetic retinopathy (DR), clinically significant macular edema (CSME) and hard exudate formation. **Materials and Methods:** In this prospective cross-sectional study carried out over a period of 2 years, type 2 diabetic patients seeking ocular evaluation for DR were assessed for presence and severity of DR, presence of hard exudates and CSME. Retinal findings were correlated to severity of microalbuminuria, hemoglobin concentration and other systemic risk factors using linear regression analysis. **Results:** Three hundred and six patients were included in the study. DR of any grade was seen in 132 (43%) patients, hard exudate formation in 93/306 (30.4%) patients, CSME in 50/306 (16.3%) patients and proliferative DR in 26/306 (8.5%) patients. Duration of diabetes ($P < 0.001$), microalbuminuria ($P < 0.001$) and low hemoglobin ($P = 0.001$) were found to be highly significant risk factors for the development and increasing severity of DR as well as for CSME and hard exudate formation. **Conclusion:** Microalbuminuria and low hemoglobin are strong predictors for DR, CSME and hard exudate formation in type 2 diabetics even after correcting for duration of diabetes and other systemic risk factors. Although not directly involved in the pathogenesis, microalbuminuria can help in identifying patients at risk for more severe diabetic eye disease. Microalbuminuria warrants intensive monitoring of both retinal and renal status. The hemoglobin levels should be monitored regularly in diabetic patients to detect and treat anemia, thereby reducing one risk factor for DR.

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Among the multiple risk factors for diabetic retinopathy (DR), the duration of diabetes is probably the strongest predictor for the development and progression of retinopathy.[1-3] Other well-known risk factors include glycemic control,[4,5] hypertension,[6] nephropathy[7] and pregnancy.[8] One of the earliest publications to recognize the link between renal and retinal angiopathy was by Root *et al*. in 1954.[8] Microalbuminuria was linked to diabetes only in 1985 when Barnett *et al*. reported an association between these two conditions.[9] This was followed by other cross-sectional and longitudinal studies reporting relationship between microalbuminuria or proteinuria with retinopathy.[10-13] Retinopathy and nephropathy are both related to endothelial dysfunction mediated microvascular complications of diabetes mellitus (DM), especially in type 1 and to a lesser extent in type 2.[13] The Microalbuminuria Collaborative Study Group report failed to project retinopathy as an independent predictor for albuminuria.[14] Hypertension as well as duration of diabetes can also confound some of the effects of renal disease on DR.[14,15]

Low hemoglobin levels are known to occur in diabetic patients with renal disease or it could coexist independently. Anemia has been shown to be associated with a more severe diabetic retinopathy.[16-18] The association of microalbuminuria and anemia with the incidence, progression and visual outcome in DR requires further evaluation. The aim of this study was to establish correlation of microalbuminuria and hemoglobin levels in type 2 diabetics with the occurrence and severity of DR and also with hard exudate formation and clinically significant macular edema (CSME).

Materials and Methods

This was a prospective cross-sectional study carried out over a period of 2 years at a multispeciality tertiary care hospital. Patients referred to the Department of Ophthalmology for the evaluation and management of DR were included in the study after obtaining informed consent. This study was approved by our institutional ethical review board.

Inclusion criteria for the study were 1) all patients with type 2 diabetes, which is defined as a fasting plasma glucose of more than or equal to 126 mg/dl or a 2-hour post glucose load plasma glucose of more than or equal to 200 mg/dl or a random plasma glucose of more than or equal to 200 mg/dl in the presence of symptoms of hyperglycemia[19] and 2) those who were physically fit to undergo a dilated fundus examination and fundus photographic evaluation. The exclusion criteria were 1) pregnancy 2) accelerated hypertension 3) active systemic infection and 4) coexisting ocular disorders like uveitis, opaque/hazy media, retinal disorders like retinal vein/artery occlusions, retinitis pigmentosa, vitreoretinal degenerations and dystrophies, high myopia and recent ocular surgeries (<6 months) including vitreo-retinal surgery for causes other than DR.

A detailed history including previous photocoagulation

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and current medication was obtained. All the subjects underwent a detailed physical and ophthalmologic evaluation. Best-corrected visual acuity (BCVA) was assessed using an illuminated Snellen's chart. The optic disc, macula and the retinal background were evaluated using indirect ophthalmoscopy and slit-lamp biomicroscopy with 78 diopter (D) lens. A stereoscopic 30° color photograph centered on the macula was obtained using TOPCON fundus camera.

The patients were divided into two groups based on the presence or absence of DR: group 0 without DR and group 1 with DR of any severity. The grading of the severity of DR was done using the modified Early Treatment Diabetic Retinopathy Study (ETDRS) protocol.[20] For purposes of analysis, patients in group 1 were subdivided as mild-moderate nonproliferative DR (NPDR), severe NPDR and proliferative DR (PDR).

Hard exudates were graded using Wisconsin Grading based on comparison of retinal photographs taken with a TOPCON fundus camera centered on the macula with the standard photographic plates 3, 4 and 5.[20] For the purposes of statistical analysis, group 1 was divided as patients with no hard exudate formation and patients with hard exudates of any severity.

CSME was diagnosed based on the modified ETDRS protocol:[21] retinal thickening at or within 500 µm of center of macula; hard exudates at or within 500 µm of center of the macula if associated with adjacent retinal thickening; zone or zones of retinal thickening 1 disc area in size, at least part of which was within one disc diameter of center of macula. For the purpose of statistical analysis, patients of group 1 were divided as those with DR without CSME and the ones with DR with CSME.

Microalbuminuria was measured by particle enhanced turbidometric inhibition assay on a spot early morning urine sample and albumin excretion for 24 hours was then calculated. Hemoglobin was assayed by electric impedance of lysed red blood cells. Other laboratory tests included fasting and 2 hour postprandial blood sugars, glycated hemoglobin (HbA1c) and lipid profile. The various risk factors evaluated in this study were defined as follows: microalbuminuria was defined as urinary albumin excretion of 30–300 mg/day;[19] hypertension was defined as a blood pressure measurement of above 140/90 mmHg in the right upper limb supine position or when the patient was on antihypertensive medication;[22] dyslipidemia was defined using NCEP ATP III guidelines as total cholesterol ≥200 mg/dl and/or high density lipoprotein (HDL) cholesterol <40 mg/dl and/or low density lipoprotein (LDL) cholesterol >100mg/dl and/or triglycerides >150mg/dl;[23] and HbA1c >7% was considered abnormal.[19]

Statistical analysis

Univariate analysis using one-way analysis of variance (ANOVA) was performed to test the association of the individual risk factors including duration of diabetes, hypertension, microalbuminuria, and hemoglobin with the occurrence of DR, its severity based on ETDRS grading, Wisconsin grading for hard exudate formation and CSME. *Post hoc* analysis using Bonferroni correction was applied for variables with more than two groups, to evaluate differences between any two groups within the variable. Those parameters which showed significant correlation ($P < 0.05$) on univariate analysis were subjected to multivariate analysis using linear regression or logistic regression (for dichotomous variables) to identify the actual significance of these variables when correcting for all confounding variables. Statistical significance was considered when P was <0.05. All analyses were done using SPSS version 10 statistical package.

Results

In this cross-sectional study, 306 type 2 diabetic patients who presented to the Department of Ophthalmology for evaluation of their DR status during the study period were included. The age of the patients ranged from 35 to 85 years, with a mean (±SD) of 56.41 (±10.1) years. The study included 193 males (61.6%) and 113 females (38.4%).

The duration of DM ranged from 1 to 30 years, with a mean (±SD) of 7.59 (±6.3) years. The occurrence of risk factors like micoalbuminuria, systemic hypertension, dyslipidemia, end-stage renal disease and insulin therapy is enumerated in Table 1.

DR of any grade was present in 132/306 (43.1%) patients. Of the 132 patients with DR, 80/132 (60.6%) had mild-moderate NPDR, 26/132 (19.7%) had severe NPDR and 26/132 (19.7%) had PDR. Of the 132 patients with any grade of DR, no gradable hard exudate formation or hard exudates less than standard plate 3 were seen in 36/132 (27.3%) patients, while 96/132

Table 1: Demographic and other systemic parameters of the study patients

Risk factor	Mean	Range (%)
Age	56.41 (± 10.01)	32–85 years
BMI	23.26 (±3.4)	15.5–35.5
Duration	7.59 (+6.3)	6 months–30 years
	Risk factor present or absent	*N* = 306 ()
BMI	<18.5 (underweight)	12 (3.9)
	18.5–23 (normal)	153 (49.8)
	23.1–27.5 (overweight))	106 (34.5)
	>27.5 (obese)	35 (11.4)
Gender	Male	193 (61.6)
	Females	113 (38.4)
Hypertension	Present	148 (48.4)
	Absent	158 (51.6)
ESRD	Present	44 (14.2)
	Absent	262 (85.8)
Dyslipidemia	Present and not treated	140 (45.8)
	Present and treated	77 (25.1)
	Absent	89 (29.1)
Insulin therapy	Present	106 (34.6)
	Absent	200 (65.4)
Anemia	Present	175 (57.3)
	Absent	131 (42.7)
Albuminuria	Absent	109 (36.0)
	Microalbuminuria	130 (42.2)
	Macroalbuminuria	67 (21.8)

BMI: Basal metabolic index, ESRD: End stage renal disease

(72.7%) had some grade of hard exudates. CSME was detected in 50/132 (37.9%) patients with DR.

The mean (±SD) Hb in patients with and without DR was 11.24 (±2.1) g/dl and 12.71 (±2.1) g/dl, respectively; mean (±SD) albumin excretion per day in patients with and without retinopathy was 688 (±99.6) g/day and 124.6 (±49.5) g/day, respectively. Duration of diabetes ($P < 0.001$), anemia ($P < 0.001$), microalbuminuria ($P < 0.001$), systemic hypertension ($P = 0.001$) and glycemic control indicated by HbA1C level ($P = 0.002$) were found to be significant risk factors for occurrence and increasing severity of DR on univariate analysis. Even on multivariate analysis, the correlation remained significant for all factors except systemic hypertension and glycemic control [Table 2].

Duration of diabetes ($P < 0.001$), microalbuminuria ($P < 0.001$) and anemia ($P = 0.002$) showed statistically significant correlation with hard exudate formation and the occurrence of clinically significant macular edema, both on univariate and multivariate analyses [Table 3]. These factors also showed statistically significant correlation with DR without CSME.

Discussion

In our study, the association of microalbuminuria with the occurrence and severity of DR, occurrence of hard exudate and CSME remained strong even after correction for duration of diabetes, one of the most important predictors of DR and other co-morbid conditions. An independent association between microalbuminuria and NPDR was observed in a study from Cameroon by Sobngwi *et al*.[24] Singh *et al*. found that increasing albuminuria was significantly associated with PDR.[25] Larger cross-sectional studies have concluded that microalbuminuria is a reliable marker for DR.[26,27] However, a recent study from Thailand has found no significant association between retinopathy and microalbuminuria.[28]

These findings support the suggestion that both DR and nephropathy progress in a parallel way. These findings stress on the need for close monitoring for DR in patients with microalbuminuria to prevent irreversible visual loss. This association also indicates the overall more grave prognosis in patients with DR, which calls for closer monitoring of renal and cardiovascular function in the presence of DR. In type 2 diabetes, unlike in type1 diabetes, microalbuminuria may not only be a marker of renal disease but also have a close association with generalized cardiovascular disease, increasing the risk of myocardial infarction or stroke.[29,30] It is also noteworthy that the body mass indices of most patients in the study were in the 18.5–23 group, confirming the lean fat phenotype of Asians with insulin resistance and increased cardiovascular risk.[31]

This study also established a correlation between DR and low hemoglobin. Low hemoglobin was an independent baseline risk factor in the EDTRS for the development of PDR and severe visual loss.[16] Other studies have corroborated this finding and have also found improvement in the DR status following correction of anemia.[17,18,32,33] Thus, the potential threat of anemia should always be taken into consideration while managing a patient with DR.

The limitations of this study include 1) the small sample size and 2) the setting of the study in a tertiary care center. Larger prospective longitudinal population-based studies are required to categorically ascertain this association of microalbuminuria and anemia with DR in type 2 diabetics.

In conclusion, we have observed a significant correlation between DR and microalbuminuria and/or lower levels of serum hemoglobin. The presence of microalbuminuria should warn the treating physician of the need to monitor the retina along with kidney function. This, in turn, may reduce the occurrence of irreversible visual loss due to DR. Low hemoglobin level, which is common in patients from

Table 2: Correlation of occurrence and severity of diabetic retinopathy with microalbuminuria, anemia and other systemic factors on univariate and multivariate analyses

	Occurrence of DR		Severity of DR	
	Univariate *P**	Multivariate *P***	Univariate *P**	Multivariate *P***
Age	0.16		0.11	
Gender	0.66		0.67	
Duration	<0.001	<0.001	<0.001	<0.001
Hypertension	0.001	0.13	0.001	0.11
Body mass index	0.47		0.57	
Glycemic control	0.002	0.01	0.09	
Microalbuminuria	<0 .000	<0.001	<0 .000	<0.001
Anemia	<0.001	0.002	<0.001	0.001

First, univariate analysis was done testing all the variables for correlation with the presence and severity of retinopathy, using one-way ANOVA. All variables having statistically significant (*$P < 0.05$) correlation with presence of retinopathy were then analyzed together as a block using linear or logistic (for dichotomous variables) regression to see if they had any effect on each other and on the presence of retinopathy (**P)

Table 3: Correlation of the hard exudates formation and clinically significant macular oedema with microalbuminuria, anemia and other systemic factors on univariate and multivariate analysis

	Hard exudates formation		CSME	
	Univariate *P*	Multivariate *P***	Univariate *P*	Multivariate *P***
Age	0.20		0.34	
Gender	0.37		0.39	
Duration	<0.001	<0.001	<0.001	<0.001
Hypertension	0.001	0.52	0.001	0.04
Body mass index	0.93		0.09	
Glycemic control	0.005		0.06	
Microalbuminuria	<0.001	<0.001	<0.001	<0.001
Anemia	<0.001	0.04	<0.001	0.002

First univariate analysis was done testing all the variables for correlation with the presence of hard exudates and CSME using one-way ANOVA and Mann-Whitney test for non-parametric data. All variables with statistically significant (*$P<0.05$) correlation with presence of retinopathy were then analyzed together as a block using linear regression to see if they had any effect on each other and on the presence of retinopathy (P**)

developing countries like India, needs to be detected and treated, thereby reducing the risk for developing DR.

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